Heterocycle Synthesis

DOI: 10.1002/ange.200700802

A General Approach to Chemo- and Regioselective Cyclotrimerization Reactions**

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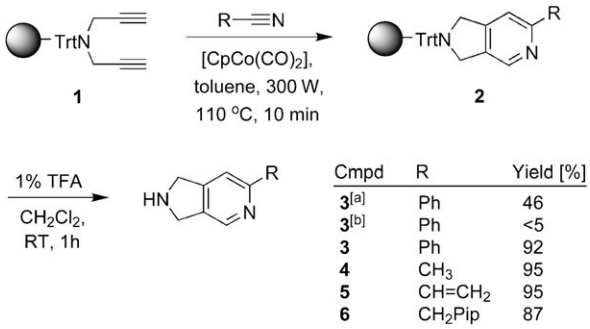
Traditional optimization of transition-metal-catalyzed reactions involves the tailoring of substrates, metals, and ligands to achieve the desired transformation with high efficiency. Here we report a more generally applicable and more practical approach to this problem through the combination of spatial separation of the substrates and microwave irradiation. We employed the [2+2+2] cyclotrimerization as an example, and thereby solved persisting reactivity and selectivity issues of this reaction. The [2+2+2] cyclotrimerization reaction is an efficient tool for the construction of carbo- and heterocyclic structures.[1,2] Traditionally, the most commonly used catalyst systems are based on cobalt and rhodium. These catalysts, in conjunction with a partially intramolecular reaction using tethered alkynes, have led to several practical applications of the [2+2+2] cyclotrimerization in the construction of fused pyridine and benzene molecules, including several total syntheses.[3] However, a variety of problems regarding classical cobalt-catalyzed [2+2+2] cyclotrimerizations for the synthesis of heterocycles still persist. These include long reaction times, high-dilution conditions, high reaction temperatures, and the necessity to activate the catalyst through irradiation with light or additives.[1] Moreover, low reactivity with certain substrates, as well as side reactions leading to complex product mixtures have been observed.[1] The recent development of Co, Ni, Rh, and Ru catalysts have led to milder reaction conditions and shorter reaction times, but often require specifically designed ligands.[4,5] Furthermore, chemoselectivity (di- and trimerization of starting materials) and regioselectivity issues are still persistent with many of the catalysts, unless specifically designed substrates are used (for example, triynes or internal diynes). As a result, no high-yielding universal approach to the [2+2+2] cyclotrimerization of a wide range of substrates has been developed to date. Herein we report a different approach to the development of highly efficient [2+2+2] cyclotrimerizations which has the potential to provide unifying conditions for other transition-metal-catalyzed cycloadditions as well. The synergistic application of microwave[6–8] irradiation and a polymeric solid support also makes the [2+2+2] cyclotrimerization highly applicable to a variety of substrates.

An initial solution-phase investigation to give the fused pyridine **3** (Scheme 1) was conducted using trityl-protected



Cmpd	R	Yield [%]
3[a]	Ph	46
3[b]	Ph	<5
3	Ph	92
4	CH_3	95
5	$CH{=}CH_2$	95
6	CH_2Pip	87

Scheme 1. Microwave-mediated solid-supported formation of fused pyridine rings. Trt = trityl, Cp = C_5H_5, Pip = piperidine, TFA = trifluoroacetic acid, gray sphere = solid support. [a] [$CpCo(CO)_2$], toluene, 110 °C, 24 h, microwave irradiation (MW, 300 W), no solid support. [b] [$CpCo(CO)_2$], toluene, 115 °C, 24 h, no MW irradiation.

dipropargylamine and benzonitrile as the starting materials. The cyclotrimerization was performed in nonpolar toluene as the solvent at 110 °C with 10 mol% [$CpCo(CO)_2$] under microwave irradiation (300 W) for 10 min. After removal of the protecting group with TFA, **3** was obtained in 46% yield (similar results have recently been observed by others[9,10]). When the same cyclotrimerization was conducted without microwave irradiation, only 9% product formation was observed, even after a prolonged reaction time of 24 h at 110 °C. Previously this has been compensated by irradiation with light, increased reaction temperatures (for example, 144 °C), addition of catalyst activating agents, and extended reaction times (up to 5 days).[11,12] The modest yield of **3** (46%) in the solution-phase cyclotrimerization is a result of the formation of benzene by-products through di- and trimerization of the diyne starting material, a problem commonly seen in cyclotrimerization reactions of reactive diynes (especially of terminal diynes).[5,13] This problem was solved through spatial separation of the diyne substrates by immobilization on a polystyrene resin.[14] We employed this strategy previously in chemoselective solid-supported cyclotrimerizations under classical conditions.[15] By using microwave heating, the immobilized diyne **1** delivered the fused pyridines **3**–**6** in excellent yields (92–95%) and high purities (>90%) after cleavage from the resin (Scheme 1). The implementation of microwave irradiation together with the

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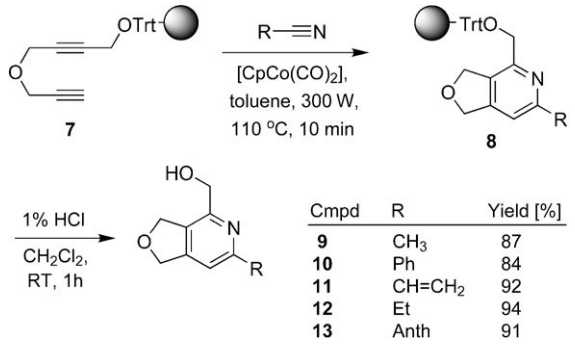
[**] We gratefully acknowledge support from the Department of Education (GAANN Fellowship to D.D.Y), the NCSU Faculty Research and Development Fund, and the Donors of the American Chemical Society Petroleum Research Fund. We thank Ramesh S. Senaiar for conducting exploratory solution-phase reactions.

Supporting information for this article is available on the WWW under http://www.angewandte.org or from the author.

solid support affords a significant increase in the yield, extremely shortened reaction times, and the elimination of catalyst activating additives, excessive heating, or irradiation with light. Interestingly, the solid-supported reaction **1**→**3** could not be performed under thermal conditions (24 h, 110 °C) and failed to yield significant amounts of product (< 5% yield). The dramatic improvement through microwave irradiation cannot be attributed just to efficient heating (in fact the reaction temperature is lower than under traditional conditions[12]), but represents one of the most pronounced examples of nonthermal microwave effects, a topic that is still controversial.[8,16] To our surprise, electron-poor nitriles could not be used in the reaction to give **2**.[17]

We initially employed the symmetrical diyne **1** to investigate the effect of the combination of microwave irradiation and a solid support, while alleviating the potential formation of regioisomers. However, to explore the ability to impose regioselectivity upon these cyclotrimerization reactions and to investigate potential effects of microwave irradiation on the regioselectivity, we selected **7** (and the structurally related **14**) as cyclotrimerization precursors for several reasons: 1) the generated products are chemically stable, 2) the possibility of using less-reactive internal double bonds will be demonstrated, and 3) the regio-inducing effect of a methylene group can be probed. Employing the previously discovered reaction conditions in the cyclotrimerization of **7** to **8** using five different nitriles afforded the fused pyridines **9**–**13** in excellent yields (87–94%) and high purities (>90%) after cleavage from the resin (Scheme 2). Most importantly,

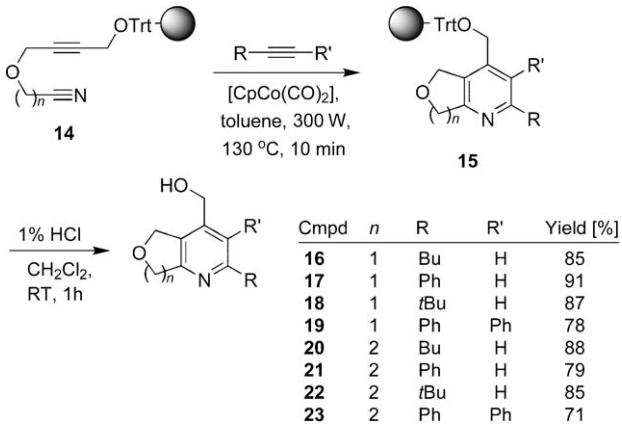


Cmpd	R	Yield [%]
9	CH_3	87
10	Ph	84
11	$CH{=}CH_2$	92
12	Et	94
13	Anth	91

Scheme 2. Solid-supported regioselective formation of fused pyridine rings under microwave irradiation. Anth = anthracene.

complete regioselectivity was obtained under microwave irradiation conditions and the obtained regioisomer is in agreement with the generally accepted cyclotrimerization mechanism for the $[CpCo(CO)_2]$ catalyst.[1]

The synthesis of positional pyridine isomers was achieved through the application of a nitrile group tethered to an alkyne.[18] Two alkynyl nitrile substrates were employed for the formation of both 5- and 6-membered fused rings. Cyclotrimerization of **14** to **15**, followed by acid-mediated cleavage from the resin, afforded pyridines **16**–**23** in high yields (73–91%), excellent purities (>90%), and as single regioisomers (Scheme 3). These yields are significantly higher than in previous solution-phase reactions (especially in the case of reactive terminal alkynes)[9,19] as competing side-



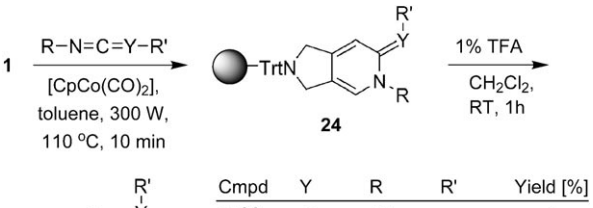
Cmpd	*n*	R	R'	Yield [%]
16	1	Bu	H	85
17	1	Ph	H	91
18	1	*t*Bu	H	87
19	1	Ph	Ph	78
20	2	Bu	H	88
21	2	Ph	H	79
22	2	*t*Bu	H	85
23	2	Ph	Ph	71

Scheme 3. Formation of fused pyridine rings from α,ω-alkynenitriles under microwave irradiation.

reactions are completely suppressed through the spatial separation on the solid support.

The cyclotrimerization of alkynes and isocyanates is an effective means of generating pyridones, and catalyst systems based on Ni, Co, Rh, and Ru have been employed.[1,17,20,21] However, these reactions either require specifically tailored substrates (for example, internal diynes or isocyanate-tethered alkynes and alkenes) or specifically tailored ligands. Reported reactions using α,ω-diynes in conjunction with $[CpCo(CO)_2]$ and [CpCo(cod)] (cod = cycloocta-1,5-diene) catalysts produce pyridones only with low efficiency.[1,20] When these cyclotrimerizations were performed under our reaction conditions, that is, a solid support in conjunction with microwave irradiation, highly efficient conversion of **1** into **25**–**27** (87–96% yield) was observed after cleavage from the resin (Scheme 4). Under classical thermal conditions (110 °C, 24 h) virtually no formation of **25** was detected (<1% yield), thus providing additional evidence for nonthermal microwave effects.

Using carbodiimides in cyclotrimerization reactions under Co and Ni catalysis provides a synthetic entry to 2-iminopyridines.[1,22] Traditionally, these reactions only show moderate chemoselectivity with respect to the formation of benzene rings and generally low yields, even when conducted with

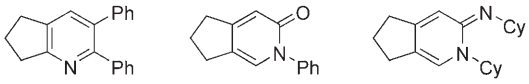


Cmpd	Y	R	R'	Yield [%]
25[a]	O	Ph	-	<1
25	O	Ph	-	93
26	O	Bu	-	96
27	O	Cy	-	87
28[a]	N	*i*Pr	*i*Pr	-
28	N	*i*Pr	*i*Pr	91
29	N	Cy	Cy	93

Scheme 4. Microwave-mediated cyclotrimerization of the diyne **1** with isocyanates, and carbodiimides. [a] $[CpCo(CO)_2]$, toluene, 110 °C, 24 h, no MW irradiation. Cy = cyclohexyl.

specifically tailored internal akynes.[22] As a result, iminopyridines have not been extensively synthesized by [2+2+2] cyclotrimerizations. Moreover, the classical [$CpCo(CO)_2$] catalyst has not been successfully employed in these reactions. We solved this problem, as demonstrated by the microwave-mediated solid-supported cyclotrimerization of **1** with carbodiimides (Scheme 4). Compound **24** (Y = N) is formed rapidly and the fused iminopyridines **28** and **29** were obtained in excellent yields (91 and 93%, respectively) and high purity (>90%). These examples demonstrate that microwave irradiation can activate otherwise inactive Co catalysts for new cyclotrimerization reactions. Again, no iminopyridine **28** could be detected under simple thermal heating (110°C, 24 h).

To validate the enhancing effects of spatial separation on the solid support, a set of microwave-mediated control reactions to give **30**–**32** (10 mol% [$CpCo(CO)_2$], toluene, 110°C, MW 300 W, 10 min) were conducted in the solution phase (a substrate concentration of 70 mM was employed, resembling solid-phase conditions). These reactions led to the



30 (16%) **31** (44%) **32** (37%)

formation of complex product mixtures, which necessitated chromatographic separation, and greatly diminished the yields (16–44%) as a result of undesired side-reactions.

In conclusion we have reported the development of microwave-mediated [2+2+2] cyclotrimerization reactions that lead to the formation of pyridines, pyridones, and iminopyridines. The mild and unifying reaction conditions enable the utilization of a wide range of substrates that deliver products in high yields, excellent purities, and with complete chemo- and regioselectivity. The universal nature of these mild reaction conditions provides a significant advantage over existing technologies, since the commercially available [$CpCo(CO)_2$] catalyst is used for all transformations, and the rapid reaction rates do not require an inert atmosphere. The observed activating effects of microwave irradiation can not be explained as simply a consequence of more effective heating, but represent pronounced examples of nonthermal microwave effects. Mechanistic explanations of nonthermal microwave effects are still in their infancy[6,8,16] and we are currently investigating the details of the observed rate enhancements. A possible explanation could be the lowering of activation barriers in the multistep cyclotrimerization mechanism[1,2] through specific dipole–dipole interactions of the electric field induced by microwave irradiation of polar intermediates (for example, metallacyclopentadienes) or polar transition states. Through this methodology, we have demonstrated the potential to employ microwave irradiation in the activation of a catalyst system for new synthetic transformations.

With the increasing prevalence of microwave reactors in synthetic laboratories, this cyclotrimerization methodology will make significant contributions to the synthesis of biologically and pharmacologically important heterocyclic molecules (for example, those based on the 4-azaisoindoline core structure), and we believe that the described approach can be applied to the optimization of other cycloaddition reactions. We observed similar enhancing effects in [2+2+2] cyclotrimerization reactions to give benzene derivatives which we will report in due course.

Experimental Section

General cyclotrimerization protocol: Derivatized resin (40 mg, 0.5–1.2 mmol g^{-1} substrate loading) was placed in a microwave reaction vessel and swelled in anhydrous toluene (500 μL) for 10 min. The soluble reaction partner (10 equiv) was added followed by [$CpCo(CO)_2$] (0.1 equiv), and the reaction was irradiated in a CEM Discover microwave synthesizer for 10 min at 300 W. The vessel was removed and the resin was washed in a syringe filter with four alternating cycles of CH_2Cl_2 and MeOH (2 mL each) The resin was dried in vacuo, transferred into a vial, and cleaved for one hour with 500 μL of a solution of either 1% TFA in CH_2Cl_2 (for **2** and **24**) or 1% anhydrous HCl in CH_2Cl_2/MeOH (3:2; for **8** and **15**). The solution was filtered through a celite plug, concentrated, and then analyzed by ^{1}H NMR spectroscopy and LC/MS.

Received: February 22, 2007
Published online: May 25, 2007

Keywords: cycloaddition · heterocycles · microwave synthesis · solid-phase synthesis · transition metals

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